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HYPERTERMIC INTRAOPERATIVE PERITONEAL CHEMOTHERAPHY FOR ADVANCED STAGE OVARIAN CANCER: DRUGS INTERACTIONS AND PHARMACOKINETIC PROFILE

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ABSTRACT:

INTRODUCTION

In advanced epithelial ovarian cancer patients, the standard of care is primary debulking surgery, followed by first-line chemotherapy often with bevacizumab addiction. In this context, some experiences have shown that a comprehensive treatment approach to surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) could improve the prognosis. Moreover Evidences from animal models seem to suggest that minimally invasive surgery may enhance cisplatin diffusion when the drug is administered in the context of post-operative hyperthermic intraperitoneal chemotherapy (HIPEC).
This is a study aimed to explore the feasibility of primary debulking surgery and HIPEC upfront followed by first-line therapy with bevacizumab. Moreover the present study evaluates the cisplatin pharmacokinetic profile in a prospective series of women with platinum sensitive recurrent epithelial ovarian cancer treated with open secondary cytoreductive surgery (O-SCS) or minimally-invasive secondary cytoreductive surgery (MI-SCS).

METHODS

Forty patients affected by advanced ovarian cancer submitted to primary debulking surgery with HIPEC were enrolled in the study. After surgery, all patients underwent systemic chemotherapy with bevacizumab addiction. PFD and OS was calculated, moreover complication rate and chemotherapy toxicity was evaluated.
In a specific patients subset, cisplatin levels were assessed at 0, 20, 40, 60, and 120 minutes in: 1) blood samples, 2) peritoneal perfusate, and 3) peritoneal biopsies at the end of HIPEC. Median C_{max} has been used to identify women with high and low drug levels. Progression-free survival (PFS) was calculated as the time elapsed between SCS+HIPEC and secondary recurrence or last follow-up visit.

RESULTS

Regarding the 40 patients enrolled complete cytoreduction (RT = 0) was achieved. Treatment-related early complications were observed in 23 patients and in 15 cases were G1-G2. Major complications were reported in 8 patients. No postoperative death was recorded. Subsequent chemotherapy was administered in all cases. Median time between surgery and first cycle of chemotherapy was 42 days (range 30-76). Concomitant bevacizumab was administered in 34 patients (85%). Maintenance with bevacizumab was feasible in 33 patients (82.5%) and its withdrawal was necessary for 1 patient (2.5%) due to G3 hypertension.
The nine (45.0%) selected women for the pharmacokinetic study women received MI-SCS, and 11 (55.0%) O-SCS. At 60 minutes, median cisplatin C_{max} in peritoneal tissue was higher in patients treated with MI-SCS compared to O-SCS (C_{max}=8.262 μg/mL vs. C_{max}=4.057 μg/mL). Furthermore, median cisplatin plasma C_{max} was higher in patients treated with MI-SCS compared to O-SCS (C_{max}=0.511 vs. C_{max}=0.254 μg/mL; p-value=0.012) at 120 minutes. With a median follow-up time of 24 months, women with higher cisplatin peritoneal C_{max} showed a longer PFS compared to women with low cisplatin peritoneal levels (2-years PFS=70% vs. 35%; p-value=0.054).

CONCLUSIONS

Data suggest that HIPEC can be safely introduced in the upfront therapy of advanced ovarian cancer.
Moreover, minimally invasive route enhances cisplatin peritoneal tissue uptake during HIPEC, further evaluations are needed to confirm the correlation between peritoneal cisplatin levels after HIPEC and survival.

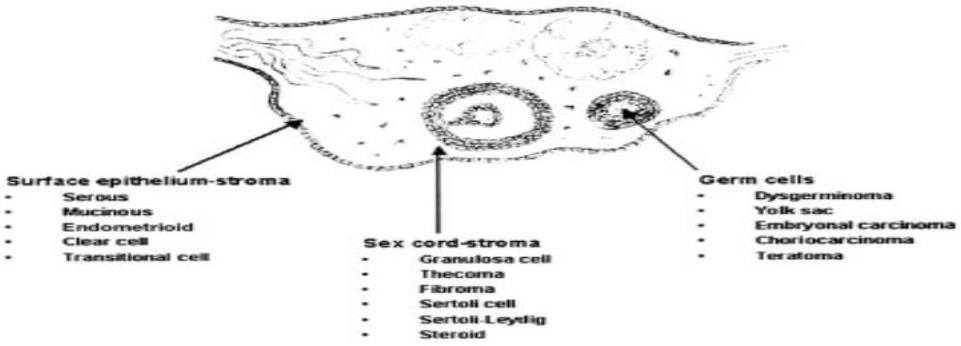
INTRODUCTION

Epidemiology

Ovarian cancer (OC) accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually [1,2]. The highest rates (11.4 per 100,000 and 6.0 per 100,000, respectively) are seen in Eastern and Central Europe. Although China has a relatively low incidence rate (4.1 per 100,000), the large population translates to an estimated 52,100 new cases and 22,500 related deaths in 2015 [3]. In comparison, 21,290 cases and 14,180 related deaths are estimated to occur in the USA during the same year [4]. A woman's lifetime risk of developing OC is 1 in 75, and her chance of dying of the disease is 1 in 100 [5]. The disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92%4. Strikingly, the overall 5-year relative survival rate generally ranges between 30%–40% across the globe and has seen only very modest increases (2%–4%) since 1995 [6].

Nearly all benign and malignant ovarian tumors originate from one of three cell types: epithelial cells, stromal cells, and germ cells **(figure 1)**. In developed countries, more than 90% of malignant ovarian tumors are epithelial in origin, 5%–6% of tumors constitute sex cord-stromal tumors (e.g., granulosa cell tumors, thecomas, etc.), and 2%–3% are germ cell tumors (e.g., teratomas, dysgerminomas, etc.) [7].

Figure 1: *Origins of the three main types of ovarian tumors.*



One of the most significant risk factors for OC is a family history of the disease [8]. First-degree relatives of probands have a 3- to 7-fold increased risk, especially if multiple relatives are affected, and at an early age of onset [9-10]. Rare high penetrant mutations in the BRCA1 and BRCA2 genes greatly increase lifetime risk [11] and account for the majority of hereditary cases and 10%–15% of all cases [12-20]. Data from the Breast Cancer Linkage Consortium suggest the risk of OC through age 70 years is up to 44% in BRCA1 families [21] and approaches 27% in BRCA2 families [26]. Hereditary non-polyposis colorectal cancer syndrome (HNPCC) [22] may account for at least 2% of cases and confer up to a 20% lifetime risk [23-27]. Women with mutations in DNA repair genes, such as BRIP1, RAD51C, and RAD51D have estimated lifetime risks of 5.8%, 5.2%, and 12%, respectively [28,29]. Deleterious mutations in BRCA1/2 and other double-strand DNA break repair genes are more strongly associated with HGSOC susceptibility although they do occur in other tumor subtypes [30-32]. HNPCC associated OC typically presents as endometrioid or clear cell tumors rather than the common serous subtype [33,34]

Pathology and classification

The pathology and classification of ovarian tumors are described in detail by Chen et al. [35].

Surface epithelial-stromal tumors are believed to originate from the surface epithelium of the ovary. They are classified as benign if they lack exuberant cellular proliferation and invasive behavior; as borderline (also known as atypically proliferating or of low malignant potential) if there is exuberant cellular proliferation but no invasive behavior; and as malignant if there is invasive behavior. Surface epithelial-stromal tumors account for approximately 60% of all ovarian tumors and approximately 90% of malignant ovarian tumors. Most borderline tumors behave clinically as benign tumors and have good prognosis, but some may recur after surgical removal and some may seed extensive implants within the abdominal cavity. Surface epithelial-stromal tumors occur primarily in women who are middle-aged or older and are rare in young adults, particularly before puberty. Five major subtypes are included within the surface epithelial-stromal group. They are designated as follows:

serous, mucinous, endometrioid, clear cell, and transitional cell (or Brenner type). Highly malignant epithelial-stromal tumors lacking any specific differentiation are classified as undifferentiated. Epithelial stromal tumors that are not designated as having a specific subtype commonly are recorded as adenocarcinomas not otherwise specified (NOS). Serous or mucinous tumors identical to those occurring in the ovary may arise in multiple locations within the pelvic and abdominal cavities. They sometimes coincide with ovarian tumors of identical type. When they do so, it may be difficult to establish whether the extraovarian sites represent seedlings or implants originating from the ovarian tumor or de novo malignancies. By convention, when the ovaries appear to be incidentally involved and do not appear to be the primary origin of the tumor, the tumor is recorded as an extraovarian peritoneal carcinoma.

Epithelial OC reflects a heterogeneous disease with histologic subtypes (histotypes) that differ in their cellular origin, pathogenesis, molecular alterations, gene expression, and prognosis [36-39]. Malignant OC, also known as carcinomas, are comprised of five main histotypes: high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (LGSOC).

The extent of tumoral spread, also known as stage of disease, at diagnosis is typically established by radiologic evaluation and surgical excision. Surgical management may include debulking of the tumor resection of one or both ovaries, fallopian tubes, and uterus, as well as sampling of lymph nodes, liver, and suspicious sites within the abdomen. Staging of ovarian surface epithelial-stromal tumors is performed according to the TNM system, the set of guidelines established by the American Joint Committee on Cancer, which is comparable to an alternative staging system approved by the International Federation of Gynecology and Obstetrics (FIGO). [40].

Intraoperatively, ovarian cancer is characterized by the widespread presence of macroscopic whitish neoplastic nodules of variable sizes and consistency, that may join together to form plaques or masses inside the abdominopelvic cavity.

Neoplastic dissemination from the peritoneal cavity into the pleural cavity may also occur, through the lymphatic lacunae within the diaphragmatic peritoneum. This results in severe pleural effusion, which compromises lung and cardiac function.

In the past, peritoneal carcinomatosis was regarded as a terminal condition and patients were treated symptomatically. However, as this disease is largely confined to the peritoneal surfaces, it is now considered to be a loco-regional disease.

Actually, Neoadjuvant Chemotherapy (NACT) followed by Interval Debulking Surgery (IDS) is a good option for patients deemed to have unresectable disease (stage IIIC/IV ovarian, fallopian tube, or primary peritoneal cancer). However, optimal debulking to microscopic disease should be achieved at the time of IDS.

From several retrospective and prospective case–control studies of NACT-ICS compared to Primary Debulking Surgery (PDS), along with recent meta-analyses, it appears that NACT-IDS offers less morbidity to patients [41,42].

Preliminary results of the prospective randomized controlled trial EORTC 55971 are consistent with the majority of the previous studies, suggesting that neoadjuvant chemotherapy followed by interval debulking results in the same survival but fewer complications than primary debulking surgery, in patients with stage IIIC/IV ovarian, fallopian tube, or primary peritoneal cancers [43].

Patients with optimal disease cytoreduction should be offered adjuvant chemotherapy for the potential survival benefit. Chemotherapy for EOC is usually given as an intravenous infusion repeatedly over 5 to 8 cycles.

EOC tends to be chemo-sensitive and confine itself to the surface of the peritoneal cavity for a long time during its natural history. These features have made it an obvious target for intraperitoneal chemotherapy, which is given by infusion of the chemotherapeutic agent directly into the peritoneal cavity. This may increase the anticancer effect with fewer systemic adverse effects in comparison to intravenous therapy.

Rationale for intra-peritoneal chemotherapy

One of the most debated arguments in the last years is the role of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in the treatment of advanced epithelial ovarian cancer (AEOC). This is considered an attractive method to deliver chemotherapy with enhanced effect directly at the tumor site.

The use of such loco-regional approach has proved to improve prognosis of peritoneal carcinomatosis from different origins (colo-rectum, appendix, pseudomyxoma peritonei and peritoneal mesothelioma) [44]. Regarding ovarian cancer, several studies have demonstrated it is able to prolong secondary disease-free survival [45,46].

A recent randomized trial by Van Driel et Al. demonstrated a significative survival improvement with comparable toxicities adding HIPEC during interval debulking surgery in patients affected by ovarian cancer [47].

However, despite these encouraging results some question actually remains unsolved, one of them is the best timing to deliver HIPEC during ovarian cancer history, especially considering that the trials available are principally focused on HIPEC administration during interval debulking surgery or during surgery for ovarian cancer recurrence. Few and not definitive data are available about HIPEC administered during primary debulking surgery.

Moreover, a pharmacokinetic profile is not actually available to determine the best dosage and method to deliver HIPEC in these subsets of patients.

The present work was focused on the evaluation of oncologic and surgical outcomes of HIPEC administered during primary debulking surgery (PDS) and consequently their interactions with new monoclonal-antibodies treatment protocols actually used [48].

The second part of the research was conducted with the aim to verify the pharmacokinetic profile of cisplatin during HIPEC administration for surgical procedures performed by laparoscopy vs laparotomy.

MATERIALS AND METHODS

Upfront HIPEC and bevacizumab-containing adjuvant chemotherapy in advanced epithelial ovarian cancer

Prospective phase II monocentric, open label, non-randomized and single-arm study, conducted at Division of Gynecologic Oncology of Agostino Gemelli Foundation IRCCS, University Hospital in Rome, from February 2015 to February 2016 and was approved by institution IRB (protocol n. 0115/2015). Informed consent was obtained from all subjects. The diagnosis was obtained at frozen section during surgery.

All enrolled patients underwent pre-operative evaluation by CT scan, pelvic ultrasound and tumor markers. Major criteria to abort PDS were the Poorest Eastern Cooperative Oncology Group performance status (i.e., ECOG-PS >2) and/ or higher American Society of Anesthesiology score (i.e., ASA >2). According to previously published data [49], all patients were submitted to Staging-LPS in order to evaluate and quantify peritoneal dissemination of the tumor through a scoring system (i.e. PIV) [50], and only patients with a score <8 were included in the final analysis.

The inclusion criteria were as follows: age between 18years and <70years; Fagotti's Score [50]<8; FIGO stage at least IIIB; ECOG-PS 2 [51]; life expectancy of at least 3 months; normal cardiac, hepatic, respiratory and bone mar- row functions (creatinine clearance >60mL/min according to Cockroft formula [52], absolute neutrophil count >1500/ml, a platelet count >150000/ml, bilirubin

levels and creatinine <1.5 times upper the range); optimal primary cytoreduction achieved (CC-0, CC-1) and signed informed consent form.

The exclusion criteria were as follows: FIGO stage less than IIIB; coexistence of other oncologic disease; body mass index (BMI) > 30 kg/m^2; active infection or general conditions that could interfere with treatment (vasculopathy, auto- immune disorders and diabetes); refusal to sign the informed consent form; previous recipient of chemotherapy treatment; distant (extra-abdominal) unresectable metastases and bowel obstruction.

The patients who met inclusion criteria, and that were considered suitable for PDS at Staging-LPS, underwent mono/bilateral adnexectomy or peritoneal biopsy to confirm the diagnosis of ovarian cancer at frozen section. If the diagnosis of ovarian cancer was confirmed, the patient was submitted to PDS with the aim to achieve complete cytoreduction (RT=0). The completeness of cytoreduction (CC) was assessed using a score ranging from 0 to 3 (CC-0 indicates no residual tumor; CC-1 indicates nodules <0.25 mm; CC-2 indicates nodules between 0.25 and 2.5 cm in diameter and CC-3 indicates nodules >2.5 cm). After completion of cytoreduction, four drains were positioned in the four abdominal quadrants. HIPEC perfusion was performed with closed technique, and the abdomen was carefully re- explored after HIPEC completion. All patients received intra- peritoneal cisplatin 75 mg/m^2 at the temperature of 41.5 ^{C} for 60 min immediately after PDS. All patients underwent systemic adjuvant chemotherapy with bevacizumab according to international guidelines [53]. Physical examination, thoracic/ abdominal CT scan and Ca 125 serum level assessment were all performed every 3 months during the first 2 years and every 6 months thereafter. Primary platinum-free interval (PFI) was defined as the time elapsed between the end of carboplatin treatment and first recurrence. Data are given as median and range. Categorical variables are reported as absolute values and percentage.

Pharmacokinetics of cisplatin during open and minimally-invasive secondary cytoreductive surgery plus HIPEC in women with platinum- sensitive recurrent ovarian cancer: a prospective study

The study included a consecutive series of 20 women with platinum-sensitive REOC receiving secondary cytoreductive surgery (SCS) plus cisplatin-based HIPEC in the context of the HORSE study, a phase III randomized clinical trial currently on going (NCT01539785, IRB No. 4794/15). The following inclusion criteria were adopted to enroll women in the present study: age over 18 and under 70 years; patients affected by a first recurrence of ovarian cancer diagnosed after 6 months from primary treatment; Eastern Cooperative Oncology Group-performance status ≤2; disease limited to the abdominal cavity with or without extraperitoneal spread considered resectable at intraoperative evaluation; adequate respiratory, hepatic, cardiac, kidney, and bone marrow function (absolute neutrophil count >1,500/mm, platelets >150,000/μL, creatinine clearance >60 mL/min according to Cockcroft formula); patient-compliant and psychologically able to follow the trial procedures. All women gave their written informed consent to be enrolled in the study, and for data and samples to be prospectively collected and analyzed.

All cases were submitted to complete blood work (blood count, chemistry, urine analysis, and cancer antigen 125 serum levels), flour-D-glucose integrated with computed tomography scan and staging-laparoscopy to exclude extra-abdominal disease and to assess the chances of optimal cytoreduction. In particular, all women with involvement of extra-abdominal sites or showing liver metastases were not considered suitable for SCS. Regarding intraperitoneal disease spread, the presence of diffuse carcinomatosis in all abdominal quadrants, the presence of stomach or mesenteric roots involvement were also considered as criteria not to proceed with SCS. All the patients fulfilling above mentioned criteria underwent optimal SCS (removal of all macroscopically detectable disease or residual intraperitoneal lesions each less than 0.25 mm) followed by platinum-based HIPEC. The extension of peritoneal spread at the time of recurrence was classified according with the peritoneal cancer index (PCI) [54].

SCS was performed through a standard open approach (O-SCS), or a minimally invasive route (MI-SCS). The choice to perform endoscopic SCS versus standard open debulking was based either on site and extension (isolated or localized vs. peritoneal carcinomatosis) of disease at relapse. In particular, MI-SCS was performed attempted only in women relapsing as single nodule in a single anatomic site, or with single nodules in different anatomic sites, while O-SCS was performed in all cases showing peritoneal carcinomatosis or diffuse relapse. Completeness of cytoreduction was defined at the end of surgery, and with abdomino-pelvic CT scan before starting planned systemic chemotherapy. Surgical complications were graded according to the Memorial Sloan Kettering Cancer Center grading system [55].

According with HORSE protocol, cisplatin-based chemotherapy was used as intraperitoneal drug. In particular, intraperitoneal cisplatin was used at a dosage of 75 mg/m^2, with a temperature of 41.5°C for 60 minutes. The drug was administered in a perfusate of saline solution in a total volume of 2,000 mL/m^2, with a perfusion speed of 600 mL/min. In all patients, closed HIPEC technique was employed, and after intraperitoneal drug delivery, the abdomen was carefully re-explored, with particular attention to hemostasis and integrity of bowel anastomoses. Systemic platinum-based chemotherapy was administered after SCS+HIPEC.

In all patients, blood samples were collected at the beginning of cisplatin-based HIPEC (T0), and at 20 (T20), 40 (T40), 60 (T60), and 120 (T120) minutes after starting HIPEC procedure. The blood taken into heparinized tubes directly from a peripheral vein was centrifuged, and plasma was transferred into cryovials. Similarly, peritoneal perfusate was retrieved at T0, T20, T40, and T60. Perfusate and plasma samples were stored at −20°C. Finally, at the end of perfusion a peritoneal biopsy was performed, and the tissue frozen in liquid nitrogen and stored at −80°C.

The entire material retrieved was finally shipped to the Cancer Pharmacology Laboratory at Mario Negri Institute for Pharmacological Research for experimental analysis respecting the frost chain.

To determine the concentration of cisplatin in the biological samples the amount of the platinum element was assayed by atomic absorption (AA) analysis using Analyst 600 (Perkin Elmer, Waltham, MA, USA) [56]. Aliquot of 200 μL of plasma or perfusate samples or 0.2g of peritoneal tissue were digested overnight with 400 μL of HNO3: HCL, then added with 600 μL of bi-distilled water, mixed and centrifuged 10 minutes at 13,000 rpm at 4°C. Aliquots of supernatant were injected into the AA instrument and assayed by means of a calibration curve made of platinum analytical standard (Sigma-Aldrich, St. Louis, MO, USA) prepared at concentrations in the range 2–200 ng/mL. The method has a limit of quantification of 2 ng/mL. The concentration of platinum was then expressed as the corresponding cisplatin concentration.

RESULTS

Upfront HIPEC and bevacizumab-containing adjuvant chemotherapy in advanced epithelial ovarian cancer

The sample size was quantified based on previous studies reporting a pooled rate of postoperative major (G3–G4) complications ranging between 45% and 98% [57] disabling an early (<40days) start to adjuvant chemotherapy (ICON 7). Based on the minimax 2-stage design by Simon [58], the null hypothesis was tested that the true rate of an early start to the administration of chemotherapy with bevacizumab after PDS and HIPEC could reach clinically relevant alternative of 85%, using an alpha-error of 0.05 and a beta-error of 0.2. Thus, the first step was planned to include 31 patients; if >25 (80%) women started adjuvant chemotherapy with bevacizumab before 40 days, the study would enroll an additional 5 patients up to a total number of 36 patients. Considering a dropout rate of 10%, at least 40 cases were planned to be enrolled. PFS was calculated from the date of diagnosis to progression of disease or the date last seen while overall survival (OS) was calculated from the date of diagnosis to the date of death of disease or the date of the last follow-up. Data analysis was

performed using the NCSS statistical software pro- gram, version 11.0 (NCSS Statistical Software, Kaysville, UT) was used.

Forty patients were prospectively enrolled. Patients' characteristics are shown in **Table 1**. The details of PDS and HIPEC procedures are shown in **Table 2.** Median surgical complexity score (SCS) was 3 (range: 2–3). Complete cytoreduction (RT=0) was achieved for all cases. Median operative time was 480 min (range: 360–740) and median Cisplatin dose was 126.5 (100–148). Median postoperative hospital stay was 8 days (range: 5–30). Diaphragm peritonectomy were performed in 67.5% while diaphragm resection in 7.5% of cases. Splenectomy was performed in 75% and 30% of patients, respectively. Pelvic/lombo aortic lymphadenectomy

Table 1. Patients' characteristics.

Variables	
All cases	40
Age (Median) (range)	51.5 (32–70)
BMI (Median) (range)	23 (18–35)
PS-ECOG (Median) (range)	0 (0–1)
Histology (N) (%)	
Serous	35 (87.5%)
Endometrioid	2 (5.0%)
Clear cell	1 (2.5%)
Stage (N) (%)	
IIIC	38 (95.0%)
IIIB	2 (5.0%)
Undifferenciated	2 (5.0%)
Grade (N) (%)	
2	3 (7.5%)
3	37 (92.5%)
PIV (LPS) (Median) (range)	4 (2–6)
PIV (LPT) (Median) (range)	4 (2–8)

were performed in 62.5% of cases only when metastatic lymph nodes were detected. Treatment-related early complications were observed in 23 patients and in 15 cases were G1–G2. Major complications consisting of pleural effusion requiring pleural drain and bowel anastomosis dehiscence were reported in five and three patients, respectively. Late complications were mild and related to kidney failure **(Table 2)**. No postoperative death was recorded.

Table 2. Perioperative outcomes.

Variables	N (%)
Surgical procedures	
Hysterectomy	37 (92.5)
BSO	40 (100)
PL/LA lymphadenectomy[a]	25 (62.5)
Omentectomy	40 (100)
Appendicectomy	14 (35.0)
LB resection	23 (57.5)
B resection	4 (10.0)
Diaphragm resection	3 (7.5)
Diaphragm peritonectomy	27 (67.5)
Splenectomy	12 (30.0)
Others	15 (37.5)
RT = 0	40 (100)
SCS[b] (median) (range)	3 (2–3)
Surgical time (min) (median) (range)	480 (360–740)
Temperature inflow (median) (range)	41.5 (41.5–43.5)
Cisplatin dose (median) (range)	126.5 (100–148)
EBL (median) (range)	600 (100–2500)
Blood transfusion	17 (42.5)
Early complications	23 (57.5)
G1–G2	15 (37.5)
G3*	5 (12.5)
G4**	3 (7.5)
Late complications	
G1	2 (5)***
G2	2 (5)***
G3	0
G4	0
Hospital stay (median) (range)	8 (5–30)

[a]https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
[b]Surgical complexity score (SCS).
*Pleural effusion (requiring drain).
**Re-laparotomy (bleeding, bowel anastomosis dehiscence).
***Two kidney failure, two kidney failure.

Subsequent chemotherapy was administered **(Table 3)** in 100% of cases (40 patients). Median time between surgery and the first cycle of chemotherapy was 42 days (range 30–76). Concomitant bevacizumab was administered in 34 patients (85%). Maintenance with bevacizumab was feasible in 33 patients (82.5%) and its withdrawal was necessary for 1 patient (2.5%) due to hypertension G3. Six out of 40 patients (15%) were not treated with bevacizumab for the following reasons: four patients experienced proteinuria and kidney failure G2 after HIPEC one patient developed central venous thrombosis and one patient showed a poor performance status after HIPEC (ECOG 2).

Table 3. Adjuvant treatment details.

Variables	N (%)
All cases	40
Chemotherapic details	
CDDP + Taxol + Bevacizumab	34 (85.0)
Bevacizumab concomitant courses (median) (range)	5 (1–6)
Bevacizumab maintenance	33 (82.5)
Bevacizumab withdrawal	1 (2.5)*
No bevacizumab administration	6 (15.0)**
Hematological toxicity	
Neutropenia G2	3 (7.5)
Neutropenia G3–G4	20 (50.0)
Anemia G3	2 (5.0)
Thrombocytopenia G3–G4	1 (2.5)
Non-hematological toxicity	
Hypertension G2–G3	3 (7.5)
Peripheral neuropathy G2	3 (7.5)

*Only one cycle for hypertension G3.
**Four patients did not receive bevacizumab due to kidney failure G2 after PDS + HIPEC; the other two patients had DVT.

At the time of this analysis, with a median follow-up of 25months (range 5–40), the progression of disease occurred in seven patients (six peritoneal progressions and one lung/ mediastinum metastasis). At present, 37 patients remain alive **(Figure 1)**.

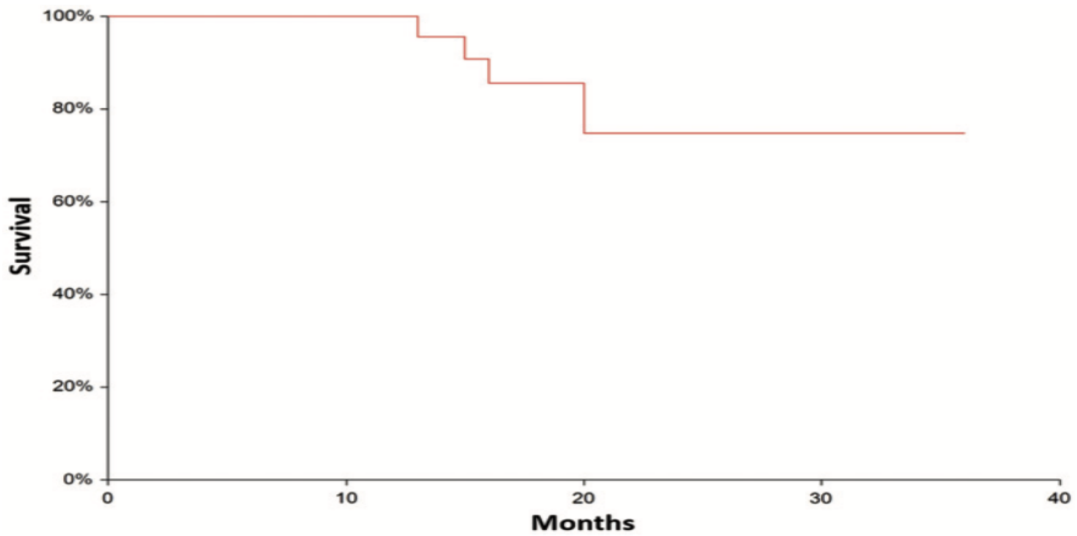


Figure 1. Overall survival in ovarian cancer patients treated with PDS and HIPEC.

Pharmacokinetics of cisplatin during open and minimally-invasive secondary cytoreductive surgery plus HIPEC in women with platinum- sensitive recurrent ovarian cancer: a prospective study

Differences between women receiving minimally invasive versus open SCS followed by HIPEC in terms of median cisplatin levels in blood, peritoneal perfusate, and tissues were analyzed using χ^2, and Kruskal-Wallis test as appropriate. Follow-up time was calculated as the time interval between SCS and last follow-up contact. Progression-free survival (PFS) was calculated as the time elapsed from SCS+HIPEC and the date of progression or last follow up. Data are given as median and range. Categorical variables are reported as absolute values and percentage. Kaplan-Meyer method was used to estimate the survival distribution [59]. All statistical calculations were performed using STATA statistical software (Version 13.0; StataCorp, College Station, TX, USA).

Between December 2013 and August 2016, 20 women with platinum sensitive REOC were enrolled in the study and received SCS plus HIPEC at the Department of Woman and Child Health of the Catholic University of Sacred Hearth of Rome. During the above- mentioned period 55 women with platinum-sensitive REOC were evaluated for inclusion in the HORSE trial, but only 49 matched inclusion criteria being finally enrolled in the trial. After randomization, 29 women were assigned to the control arm receiving surgery without HIPEC, and the remaining 20 patients were enrolled in the experimental arm including debulking surgery followed by HIPEC, and these patients represent the final population of the current pharmacokinetic study. Among this group of women, in 9 (45.0%) patients SCS was successfully completed through a minimally invasive approach (MI-SCS), while the remaining 11 (55.0%) patients were submitted to the traditional O-SCS. In all cases complete cytoreduction with no gross residual disease has been achieved.

The clinico-pathological characteristics of the study population have been presented in **Table 4**. The median age of the study population was 51 years (range, 30–66) without differences between the 2 groups, and all patients showed high-grade serous ovarian cancer. Similarly, no differences were

observed in term of cisplatin dosage, and volume of perfusate administered during HIPEC between the 2 treatment arms. The median PCI was 3 (range, 2–12) in the O-SCS group compared with 2 (range, 2–5) in women receiving MI-SCS (p-value=0.119). A very favorable toxicity profile has been observed with the vast majority of women showing no complication (**Table 4**), and only 2 patients experiencing a grade 3 adverse event (pleural effusion requiring chest drainage placement, and acute renal failure due to post-operative hydronephrosis resolved with sequelae).

Table 4: Distribution of patients' clinical-pathological characteristics of the study population

Characteristics	All patients	O-SCS+HIPEC	MI-SCS+HIPEC	p-value*
All cases	20	11 (55.0)	9 (45.0)	-
Age (yr)	51 (30–66)	51 (30–66)	49 (43–62)	0.675
Site of recurrence				0.065
Peritoneum alone	12 (60.0)	9 (81.8)	3 (33.3)	
Peritoneum+other	8 (40.0)	2 (18.2)	6 (66.7)	
PCI	2 (2–12)	3 (2–12)	2 (2–5)	0.119
Cisplatin dosage (mg)	125 (122–142)	125 (123–142)	124 (122–130)	0.220
Total perfusate volume (mL)	3,320 (3,240–3,780)	3,320 (3,280–3,780)	3,300 (3,240–3,460)	0.224
Early post-operative complications after SCS+HIPEC†				0.728
None	16 (80.0)	8 (72.7)	8 (88.9)	
G1–2	2 (10.0)	2 (18.2)	0	
G3	2 (10.0)	1 (9.1)	1 (11.1)	
PFI-1(mo)‡	21 (6–60)	20 (6–60)	24 (9–39)	0.995
Secondary recurrence				0.574
Yes	6 (30.0)	3 (27.3)	3 (33.3)	
No	14 (70.0)	8 (72.7)	6 (66.7)	
3-yr PFS (CI)‡	60.5 (19.1–85.5)	58.3 (15.7–85.4)	70.6 (22.9–92.1)	0.957
PFS>PFI-1	11 (55.0)	7 (63.6)	4 (44.4)	0.342

Values are presented as median (interquartile range) or number (%).CC, completeness of secondary cytoreduction; CI, confidence interval; HIPEC, hyperthermic intraperitoneal chemotherapy; MI-SCS, minimally invasive secondary cytoreductive surgery; O-SCS, open secondary cytoreductive surgery; PCI, peritoneal cancer index; PFI-1, primary platinum-free interval; PFS, progression free survival (time elapsed from SCS+HIPEC to disease progression or last follow-up); PRS, post-relapse survival (time elapsed from SCS+HIPEC to death or last follow-up).
*Calculated by χ^2 test, and Kruskal-Wallis non-parametric test as appropriate; †Complications have been classified according to Memorial Sloan Kettering Cancer Center grading system; ‡Calculated according with Kaplan-Meier method.

Pharmacokinetics results

At all the time points, we documented a higher, cisplatin perfusate concentration in women receiving MI-SCS compared to patients treated with the open route (**Table 5**). Notably, at each of the time point monitored, the median perfusate cisplatin concentration was largely above the cytotoxic threshold (10 μg/mL). The higher perfusate concentration measured after MI-SCS generated also a superior drug exposure in the peritoneal tissue in this cohort of women, being median peritoneal concentration of cisplatin of 8.262 μg/mL, higher than 4.057 μg/mL measured in women receiving laparotomic surgery.

As concerning the systemic exposure of the HIPEC treatments, the median cisplatin plasma concentration, increased progressively during perfusion reaching the C_{max} at 60 min after the beginning of HIPEC (T60=0.494 µg/mL). It is to note that comparing plasma concentration according with surgical approach, women receiving MI-SCS showed higher plasma exposure compared to patients treated with O-SCS; however, these differences reached statistical significance only at T120 (**Fig. 2**). In fact, 2 hours from the beginning of cisplatin-based HIPEC, the patients treated through a minimally invasive route showed double cisplatin plasma levels compared to women receiving the traditional laparotomic surgery (MI- SCS=0.511 vs. O-SCS=0.254 µg/mL; p-value=0.012).

Table 5: Pharmacokinetic results of cisplatin according with surgical approach

Characteristics	All patients	O-SCS+HIPEC	MI-SCS+HIPEC	p-value*
C_{max} plasma (µg/mL)				
T0	-	-	-	-
T20	0.362 (0.026–1.41)	0.332 (0.026–0.678)	0.442 (0.098–1.410)	0.119
T40	0.450 (0.15–1.71)	0.411 (0.233–0.639)	0.506 (0.15–1.710)	0.270
T60	0.494 (0.176–1.338)	0.446 (0.212–0.646)	0.552 (0.176–1.338)	0.305
T120	0.324 (0.175–1.225)	0.254 (0.175–0.345)	0.511 (0.257–1.225)	0.012
C_{max} perfusate (µg/mL)				
T0	22.572 (8.869–43.394)	21.377 (13.352–43.394)	27.665 (8.869–38.778)	0.477
T20	20.058 (6.245–28.902)	13.186 (6.245–28.902)	20.492 (7.677–28.442)	0.409
T40	16.341 (8.782–31.542)	12.318 (8.782–27.000)	17.738 (9.030–31.542)	0.239
T60	12.309 (6.885–29.372)	10.729 (6.885–18.415)	16.274 (8.085–29.372)	0.120
C_{max} peritoneum (µg/mL)	6.704 (1.477–27.411)	4.057 (1.477–27.411)	8.262 (1.970–22.149)	0.386

Values are presented as median (interquartile range).
HIPEC, hyperthermic intraperitoneal chemotherapy; MI-SCS, minimally invasive secondary cytoreductive surgery; O-SCS, open secondary cytoreductive surgery.
*Calculated by Kruskal-Wallis non-parametric test.

Figure 2: cisplatin exposure MI-SCS vs O-SCS

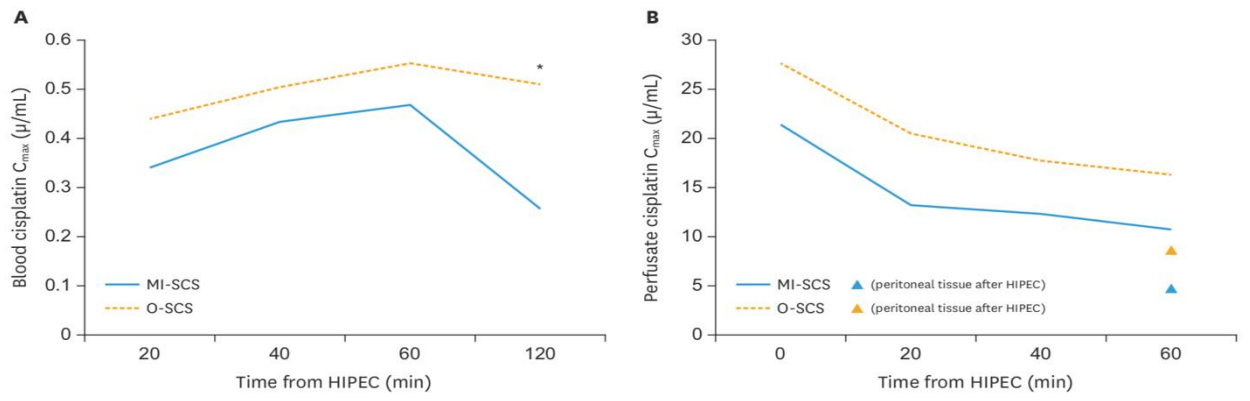


Fig. 2. (A) Blood cisplatin C_{max} at each time point during and after HIPEC in women receiving O-SCS (solid line), and MI-SCS (dashed line). Asterisk refers to the only time point (T120) showing a statistically significant difference (p-value=0.012). (B) Perfusate cisplatin C_{max} at each time point during HIPEC in women receiving O-SCS (solid line), and MI-SCS (dashed line). Black triangle indicates cisplatin peritoneal levels after HIPEC in women receiving O-SCS. White triangle indicates cisplatin peritoneal levels after HIPEC in women receiving MI-SCS.
HIPEC, hyperthermic intraperitoneal chemotherapy; MI-SCS, minimally invasive secondary cyotreductive surgery; O-SCS, open secondary cytoreductive surgery.

At December 2017, the median follow-up time of our study population (calculated from the date of HIPEC administration to last follow-up) was 24 months (ranging from 14 to 43 months). As reported in **Table 4**, 3-years PFS was 60.5% in the overall series, with 6 women experiencing secondary recurrence (30.0%) without differences according with surgical route of SCS. Interestingly, 55% of women included in the study showed a PFS longer than primary platinum-free interval (PFI-1) (**Table 4**). To assess whether a correlation may exist between pharmacokinetic variables and PFS, we used the median value of each parameter as the threshold to identify women with high, and low levels. As presented in **Table 6**, peritoneal cisplatin C_{max} significantly correlated with duration of PFS. In particular women with higher cisplatin peritoneal C_{max} showed a longer PFS compared to women with low peritoneal levels of the drug (2-years PFS=70% vs. 35%; p-value=0.054; **Fig. 3**).

Table 6: Correlation between pharmacokinetic parameters and PFS

Characteristics	2-years PFS (%)	p-value*
C_{max} plasma T20		0.628
High	55	
Low	50	
C_{max} plasma T40		0.547
High	54	
Low	55	
C_{max} plasma T60		0.342
High	66	
Low	43	
C_{max} plasma T120		0.589
High	63	
Low	63	
C_{max} perfusate T20		0.940
High	58	
Low	50	
C_{max} perfusate T40		0.611
High	58	
Low	26	
C_{max} perfusate T60		0.908
High	56	
Low	50	
C_{max} peritoneum		0.054
High	70	
Low	35	

PFS, progression-free survival.
*Calculated with log-rank test.

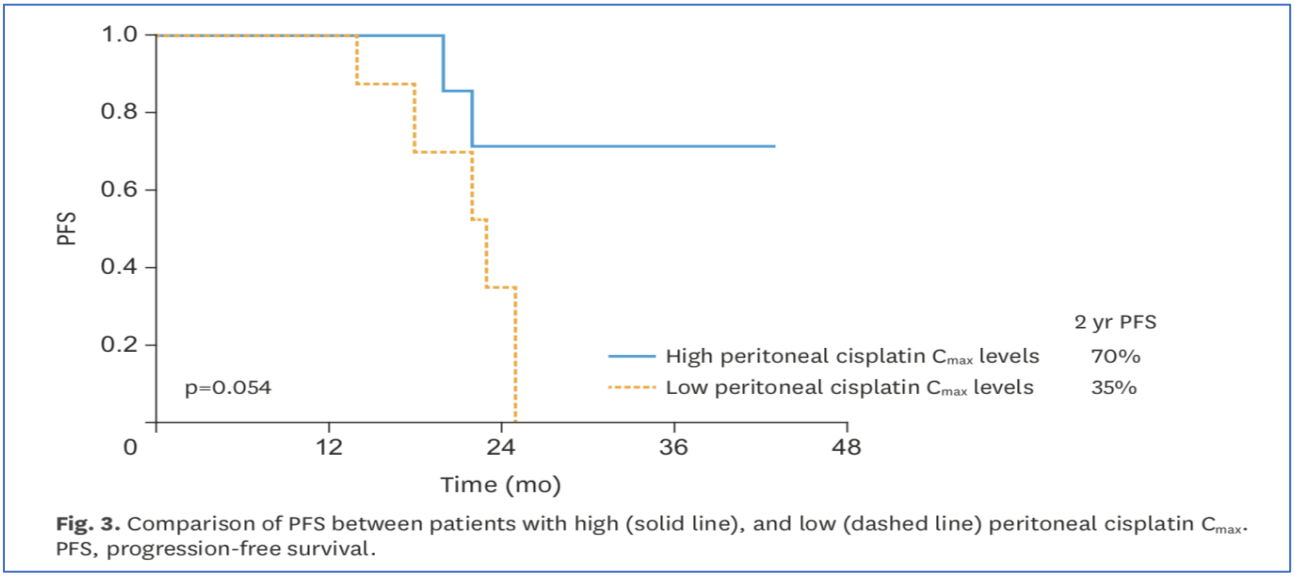


Fig. 3. Comparison of PFS between patients with high (solid line), and low (dashed line) peritoneal cisplatin C_{max}. PFS, progression-free survival.

DISCUSSION

Primary debulking surgery followed by chemotherapy is the cornerstone of AEOC treatment. The addiction of the biological anti-angiogenic agent as bevacizumab to standard chemotherapy resulted in a prolongation of PFS, consequently the combination of carboplatin, paclitaxel and bevacizumab became the new standard in the first-line treatment of AEOC [60]. However, survival results in ovarian cancer remain largely unsatisfactory. In this context, HIPEC has been proposed as a promising strategy based on several theoretical reasons: 1) i.p. chemotherapy is certainly effective in the management of AEOC, as reported in a randomized clinical trial [47]; (ii) hyperthermia has proved to enhance cytotoxicity of platinum compounds [61] and (iii) starting chemotherapy at surgery virtually avoids any delay in chemotherapy. This last reason could be particularly significant because it has been demonstrated that a delay of 7 days in beginning chemotherapy resulted in an 8.7% increase of mortality in patients with complete surgical debulking [62].

In our study, we have found that PDS with HIPEC is feasible and can be combined with the most active primary therapy presently available in AEOC, i.e., carbo-taxol bevacizumab. Despite the aggressive surgical procedures performed, toxicity was mild and easily managed (20% of G3–G4

morbidity) with a median hospital stay of 8 days. This result is relevant because the risk of increased postoperative complications after primary debulking surgery and carboplatin-paclitaxel-bevacizumab adjuvant chemotherapy was raised as a potential issue in the management of AEOC based also on experiences in colorectal cancer treatment. Interestingly, as reported by Duska et al. [63] the addition of bevacizumab to conventional first-line regimen does not imply an increased risk of readmission or postoperative complications. As the subgroup of patients experiencing multiple readmissions (>2) only accounted for around 3% of the entire population, the use of bevacizumab seems to be detrimental. Furthermore, the paper by Duska et al. [63] is also highly valuable to identify the correct time interval between primary cytoreductive surgery and adjuvant chemotherapy. In particular, given the observation that patients readmitted within 40 days of surgery had a significantly shorter interval from surgery to chemotherapy initiation (22 versus 32days, $p < .0001$), 40 days seems to be the gold standard time-interval to be respected prior to starting adjuvant carboplatin- paclitaxel-bevacizumab chemotherapy. In our series, the median time to start chemotherapy of 42 days suggests that HIPEC addiction does not influence the ideal time to start chemotherapy.

As far as the combination of HIPEC and bevacizumab in ovarian cancer, our data are consistent with the recent paper by Gouy et al. [64] which demonstrated that bevacizumab maintenance treatment could be safely completed on around one-third of patients, with six cycles of carboplatin-paclitaxel-chemotherapy followed by IDS and HIPEC. Interestingly, this percentage is completely in line with results from the GOG- 0218 trial, suggesting that even an aggressive multimodal approach combining neoadjuvant chemotherapy (NACT), IDS and HIPEC does not affect the chance of successfully complete bevacizumab-maintenance therapy without enhanced toxicities [48].

At present, there is still no consensus in the actual indication to perform HIPEC in ovarian cancer. Despite several studies seems suggest a benefit of HIPEC treatment in ovarian cancer and new technologies are now available [65], no conclusions can yet be drawn. This is due to several limitations and biases of the studies available, which consist of small single institution and not

homogeneous series utilizing different drug dosage/schedule and time of exposure in different clinical settings. Recent results of a randomized phase III study suggested that HIPEC at IDS might improve survival of patients undergoing neoadjuvant chemotherapy [47]. Thanks to the study the use of HIPEC only at the time of IDS is actually a treatment option according with NCCN guidelines 2019.

However, while waiting for the conclusion of several other randomized trials currently in progress (HORSE NCT01539785, CHORINE NCT01628380 and MMC 2014 NCT02124421), one RCT [47] and one case-control [66] study suggest a potential role of HIPEC in the improvement of patient prognosis at Interval debulking surgery and recurrent ovarian cancer, respectively. Finally, in a recent systematic review and meta-analysis of 37 studies in ovarian cancer by Huo et al. [57], the combination of HIPEC with cytoreductive surgery plus adjuvant chemotherapy, showed significantly better survival compared with cytoreductive surgery plus adjuvant chemotherapy alone. The improved results were reported both for upfront and recurrent settings.

The data reported in the present research suggest that HIPEC can be safely introduced even in the upfront therapy of AEOC consisting of primary debulking surgery and carbo-taxol-bevacizumab chemotherapy.

Considering all data reported the safety profile and absorption of cisplatin administration remain a controversial argument. And actually, the risk of increased toxicity still represents the main limitation to the introduction of HIPEC into routine clinical practice.

Focusing on the secondary objective of the research, was demonstrated that women receiving HIPEC through a minimally invasive approach reach double cisplatin peritoneal tissue levels compared to patients submitted to open cytoreductive surgery (O-SCS). Furthermore, a statistically significant higher plasma concentration of the drug 2 hours after HIPEC beginning in the Minimally invasive secondary cytoreductive surgery (MI-SCS) was observed compared with the (O-SCS) group. However, the higher blood cisplatin levels (T60=0.553 μg/mL) observed in the MI-SCS group were

below the threshold of drug cytotoxicity (10 μg/mL) [67]. Therefore, the data suggest that the minimally invasive route, even increasing drug absorption, does not modify the systemic cisplatin toxicity profile, but it allows at the same time to reach very high intraperitoneal drug concentrations (perfusate C_{max} in MI-SCS group ranging from 16.274 to 27.665 μg/mL), thus improving the overall therapeutic index of cisplatin during intraperitoneal administration. In this context, it could be inferred that the described pharmacokinetic results may be related to a higher initial cisplatin dosage in women receiving MI-SCS. However, the lack of differences in terms of drug concentration, and perfusate volume between the 2 groups (**Table 5**) further supports the hypothesis that the surgical approach (endoscopy versus laparotomy) may influence cisplatin pharmacokinetic profile in women receiving SCS plus HIPEC.

It should be emphasized that the research confirms, for the first time in humans, the results previously observed in animal models. In fact, Gesson-Paute et al. [68,69] reported an increased oxaliplatin amount crossing through the peritoneal barrier, with a higher drug diffusion in the omentum, peritoneum, and liver in pigs receiving HIPEC through the minimally invasive approach compared to animals submitted to laparotomic HIPEC. A potential explanation to our results could be found in experimental data suggesting that the increase of intra-abdominal pressure enhances drug penetration, and blood absorption in rat models [70,71]. Therefore, it is reasonable to hypothesize that the integrity of the abdominal wall during HIPEC after MI-SCS allows to reach a higher intraabdominal pressure compared to the traditional laparotomic procedure, thus enhancing cisplatin crossing though the peritoneal/plasma barrier. The clinical implications of these findings have not to be underestimated, since the demonstration that endoscopy enhances the cisplatin blood absorption in REOC patients gives a strong rationale to actively test, and further develop novel techniques of intraperitoneal drug administration, such as pressurized intraperitoneal chemotherapy [72-74] or hybrid technologies [75,76], able to provide at the same time intraperitoneal pressure modulation, hyperthermia, and drug perfusion.

Another relevant finding of the research is the observation of a longer PFS in Recurrent epithelial ovarian cancer (REOC) patients showing higher peritoneal cisplatin levels after SCS+HIPEC. Looking carefully at experimental data, it is well known, since its first preclinical development, that the cytotoxic effect of cisplatin depends on its concentration and on the length of cancer cells exposure to the drug [77]. Furthermore, more recently, it has been demonstrated a longer survival in mice with peritoneal disseminated gastric cancer receiving intraperitoneal pegylated cisplatin [78], thus confirming in animal models that an increased penetration and exposure of cancer cells to cisplatin may ensure a survival benefit. In this context, it should be acknowledged that the small sample size, and the short duration of median follow-up time in our series do not allow drawing definitive conclusions regarding oncological outcome. However, it appears reasonable to hypothesize that microscopic tumor foci have been more effectively controlled in those patients showing higher cisplatin peritoneal levels after HIPEC (threshold of 6.704 μg/mL corresponding to the median value of our series), thus ultimately resulting in a prolonged PFS (2-years PFS 70% vs. 35%; p-value=0.054). In this context, our data offer potential explanations to contrasting results obtained from RCTs on the role of dose-dense chemotherapy in AOC [79].

The results of present research need to be confirmed in further studies expanding sample size and improving reliability of these results. On the other hand, the study demonstrates for the first time that the minimally invasive route enhances cisplatin blood absorption in women receiving HIPEC, thus providing a strong rationale to further develop novel strategies of endoscopic intraperitoneal drug administration in REOC patients with locoregional disease. If further confirmed the observed borderline correlation between peritoneal cisplatin levels after HIPEC and survival may open the route for the development of novel therapeutic strategies.

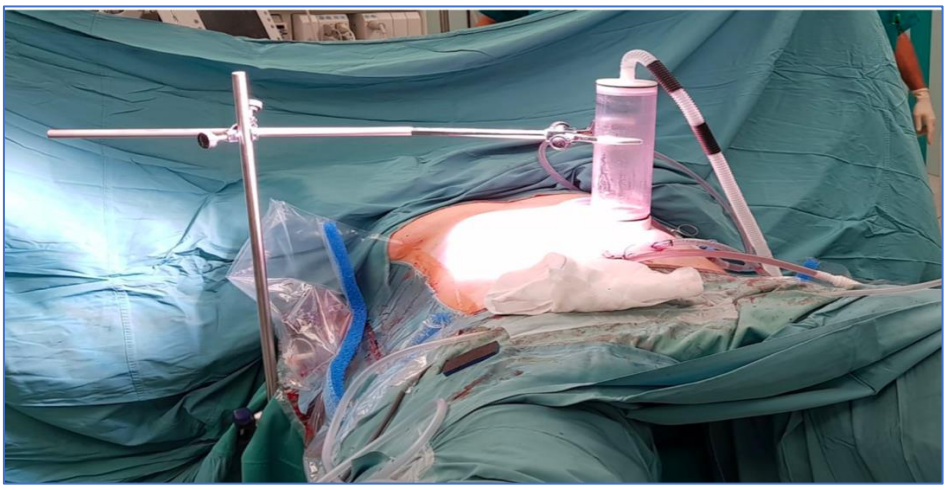
Future perspectives

Considering the available data regarding the advantages of enhanced intra-abdominal pressure during HIPEC in terms of chemotropic absorption new technologies are actually available. New techniques and devices available for intraperitoneal delivery of chemotherapy are principally PIPAC (Pressurized Intra Peritoneal Aerosol Chemotherapy) [73, 74] and Peritoneal Recirculation System (PRS-1.0 Combat) with CO2 technology [75,76].

PRS consists of a hybrid technique in which chemotherapy infusion is in a liquid status with the addition of CO_2 that amplifies the intra-abdominal fluid circulation. This new technology consisted of two roller pumps and a warm external reservoir for heating the perfusate solution, two inflow tubes, two outflow tubes and another tube used for CO_2 infusion [75,76].

The advantage of this technique is the presence of a reservoir (Fig. 4) that allows to verify the level of intraperitoneal solution and consequently to confirm that the abdomen is completely filled. Moreover, the presence of CO_2 could allow creating a sort of intraperitoneal circulation with the aim to create a more homogeneous drug distribution.

Figure 4: PRS system



A preliminary single arm prospective pilot study was conducted at Policlinico Agostino Gemelli Foundation, IRCCS, University Hospital, Rome, from July 2017 to May 2018 seventeen patients affected by peritoneal carcinosis from different origin as ovarian, gastric and colorectal cancer were enrolled to value the feasibility of HIPEC procedure with PRS technology. Patients' characteristics are reported in **Table 7**.

Table 7: Patients' carachteristics

Cases *N.* 17	Median
Age	54 (range 38–74)
BMI	24 (range 18–34)
ECOG	0 (range 0–1)
Ovarian cancer (first diagnose)	1 (5.8%)
Ovarian cancer recurrence	8 (47.0%)
Appendiceal cancer	6 (35.2%)
Colorectal cancer	1(5.8%)
Gastric cancer	1(5.8%)
Stage	
III	11 (64.7%)
IV	6 (35.2%)
PCI	7 (range 0–20)
Histotype	
Serous	9 (52.9%)
LAMN	4 (23.5%)
Adenocarcinoma	4 (23.5%)
Grade	3 (1–3)

Complete cytoreduction (RT = 0) was achieved for all cases. Median operative time was 420 min (range: 335–665) and median drugs dose used for HIPEC was 137 mg/m2 (115–756). Median EBL was 200 ml (range 50–1000). Median post-operative hospital stay was 9 days (range: 4–24). Treatment- related early complications (within 30 days from surgery), according with Dindo classification [80], were recorded in 8 (47.0%) cases and were G1–G2 consisting in urinary infection treated with antibiotics, pleural effusion and increased creatinine levels spontaneously solved **(Table 8)**. Major complications occurred in 2 (11.7%) cases, bowel anastomosis dehiscence and pelvic

abscess required readmission in operative room for colostomy and abscess drainage, respectively. Late complications (after 30 days from surgery) were related to one case of bowel obstruction required ileostomy. No post-operative death was recorded. Subsequent systemic chemotherapy was administered in 100% of cases.

Table 8: peri-operative outcomes

	Median—*N*
RT 0	17 (100%)
EBL (ml)	200 (range 50–1000)
Operative time (min)	420 (range 335–665)
HIPEC drugs	8 (47.0%) cisplatin (60 min)
	1 (5.8%) cisplatin + taxol (90 min)
	8 (47.0%) oxaliplatin (30 min)
HIPEC drug dosage (mg/m2)	137 (range 115–756)
Post-operative complications	
Grade 1–2	8 (47.0%)[a]
Grade 3–4	2 (11.7%)[b]
Hospital stay (days)	9 (4–24)

[a]Urinary infection, pleural effusion, creatinine enhanced, rectal bleeding
[b]Bowel anastomotic leak, pelvic abscess

Considering the aim to test the PRS in different cases and in different pathologies the results confirmed that the technique in feasible with good perioperative outcomes. However, considering the nature of the study as preliminary experience, the sample is not sufficient to give definitive conclusions. Moreover, other studies are needed to confirm even the oncologic outcomes;

In recent years the role of Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in cases of peritoneal metastases in platinum-resistant and non-surgical patients is increasingly being considered even in cases of gynecological tumors [73].

The PIPAC rationale is the high-pressurized administration of chemotherapy (Cisplatin and Doxorubicin for ovarian cancer) using aerosol to induce apoptosis of peritoneal neoplastic cells, despite chemoresistance. The high pressure allows a greater diffusion of the substance on all

peritoneal surfaces, as demonstrated by Solass et al. and Petrillo et Al. [81,82], increasing the tumor rate exposed to the anti-neoplastic agent. Moreover, several authors reported a greater drug penetrance and drug tissue concentration after PIPAC compared to the classical peritoneal liquid chemotherapy [83,84].

This is also due to an intra-abdominal pressure increasing during the procedure which causes a lower venous back-flow to the heart and therefore a greater permanence of the drug on the peritoneum and therefore in contact with the tumor [85]. Despite the preliminary encouraging results reported on the use of PIPAC in ovarian cancer, it is currently considered, only in selected centers and in clinical trials context. Considering that to date large randomized or prospective studies on the role of PIPAC in ovarian cancer are still ongoing.

CONCLUSIONS:

Intra peritoneal chemotherapy for the treatment of AEOC is actually a valid treatment alternative. Off course it does not avoid systemic chemotherapy but have a synergic mechanism. There are different technologies that enhance the intra-abdominal pressure during procedure with the aim, as demonstrated, to amplify the drugs absorption. Considering that even if the advantages are well demonstrated some questions remain contrivers as the best time to deliver HIPEC during natural history of the pathology and the best dosage. More investigations are needed.

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